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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CHANG-YI LIN, YUNN-TZER LU, and DEAN-MO LIU

Appeal 2011-000729
Application 10/800,622
Technology Center 1600

Before DONALD E. ADAMS, FRANCISCO C. PRATS, and STEPHEN WALSH, *Administrative Patent Judges.*

PRATS, *Administrative Patent Judge.*

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to an apatite-containing pharmaceutical dosage form. The Examiner entered rejections for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

Claims 1-16, 18-20, and 72 stand rejected and appealed (App. Br. 2).[1] Claim 1, the only independent claim, is representative and reads as follows:

> 1. A stable and taste masked pharmaceutical dosage form comprising porous apatite grains and a drug entrapped in pores of said grains, wherein said grains have a size of 0.1-1000 pm and said pores of said grains have an opening of 0.5-300 nm, and said dosage form further comprising a biocompatible polymer, wherein said porous apatite grains are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm.

The following rejections are before us for review:

(1) Claims 1-11, 14, 15, 18-20, and 72, under 35 U.S.C. § 103(a) as obvious over Tsuru,[2] Lee,[3] and Isobe[4] (Ans. 3-7); and

(2) Claims 12 and 13, under 35 U.S.C. § 103(a) as obvious over Tsuru, Lee, and Makoto[5] (Ans. 7-8).

OBVIOUSNESS

The Examiner found that Tsuru disclosed slow release drug delivery dosage forms that contained porous granules of calcium phosphate, which could be in the form of hydroxyapatite, but which differed from claim 1's composition in that "Tsuru did not disclose binding of the granules into [a]

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[1] Appeal Brief entered February 23, 2010.
[2] EP 0 376 331 A2 (published July 4, 1990).
[3] WO 00/15194 A1 (published March 23, 2000).
[4] U.S. Patent No. 5,603,945 (filed February 17, 1994).
[5] Makoto Otsuka et al., *Effect of Sodium Bicarbonate Amount on In Vitro Indomethacin Release from Self-Setting Carbonated-Apatite Cement*, 14 PHARMACEUTICAL RESEARCH 444-449 (1997).

composite using a biocompatible polymer" (Ans. 5). To meet that deficiency, the Examiner cited Lee as disclosing adjuvant compositions in which apatitic particles were combined with a biocompatible polymer, such as polylactic acid or polyglycolide, to increase the adjuvant activity of the particles (*id.* at 5-6).

Thus, the Examiner reasoned, an ordinary artisan would have considered it obvious to "use poly-L-lactic acid and/or polyglycolide (PGA) to the granules disclosed by Tsuru to add adjuvanticity and/or resorbability to an oral tablet made from the granules disclosed by Tsuru" (*id.* at 6). The Examiner cited Isobe as evidence that the features of claim 9, which ultimately depends from claim 1, would also have been obvious to an ordinary artisan (*id.*).

Appellants argue that the Tsuru is deficient as compared to claim 1 for a number of reasons unrecognized by the Examiner (App. Br. 5-8; *see also* Reply Br. 2-4). Moreover, Appellants argue, because Lee's disclosure of combining polymers with apatite particles is for the purpose of increasing the adjuvant properties of the particles, Lee does not remedy the deficiencies of Tsuru (*see* App. Br. 8-9; Reply Br. 4). Appellants urge that Isobe does not remedy the shortcomings of the other two references (*see* App. Br. 10; Reply Br. 5).

We agree with Appellants that the Examiner has not made a prima facie case of obviousness.

While the Supreme Court has emphasized "an expansive and flexible approach" to the obviousness analysis, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007), the Court also reaffirmed the importance of determining "whether there was an apparent reason to combine the known

elements in the fashion claimed by the patent at issue." *Id.* at 418 (emphasis added).

Ultimately, therefore, "[i]n determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

Here, Tsuru focuses on implanted or injected compositions that slowly release chemotherapeutic agents from porous calcium phosphate granules in a controlled manner (*see* Tsuru, abstract; *see also, id.* at 4-5 ("[T]he application of slow release drug delivery granules is also not limited to specific methods, and include, for example, a local injection or application as an implantation tablet or a filler, in addition to the transvascular chemotherapy.")).

In contrast, Lee focuses on the use of calcium phosphate granules as adjuvants for increasing the efficacy of vaccines (Lee at 7 ("The present invention provides calcium-containing adjuvants and vaccine delivery vehicles which, when present when alone or in combination with one or more active agents such as antigens or vaccines, elicit a host response or augment a host response towards the antigen of vaccine.")).

We acknowledge that, in addition to the primary focus of increasing vaccine efficacy, Lee discloses that its "inventive adjuvants or delivery vehicles may provide continuous, delayed, sequential and/or intermittent depot delivery of an antigen or other active agent to a host. In other cases the material may deliver a quick one-time dose of an active agent to a host" (*id.*).

However, when Lee discloses combining its calcium phosphate particles with polymers, Lee discloses that the purpose of that combination is to increase the antigenicity of the resulting composition, so that a vaccine containing the antigen will be more effective:

> Liposomes and polymers (e.g. PMMA, PLGA, PLA, gelatin, poly(phosphazene)), particularly biodegradable polymers, may also increase adjuvant activity by themselves serving as a delivery vehicle for the inventive calcium phosphate adjuvant. Additionally, liposomes and polymers are considered to have adjuvant potential . . . . In a preferred embodiment, a liposome or polymer will encapsulate the calcium phosphate adjuvant, producing microspheres. Methods of encapsulation, using polymers and liposomes, are well known to those skilled in the art. The size of the microspheres is controlled during manufacturing. The coordinated use of smaller microspheres (10 μm) and larger microspheres (> 10 μm) will create the pulsatile kinetics of antigen release typically seen with primary and secondary immunizations and boosters, respectively. The antigen may be combined (incorporated or adsorbed) with the liposome or polymer, the calcium phosphate adjuvant or both. The calcium phosphate/liposome adjuvant may also entrap any substance that will improve the vaccine, such as desired cytokines, other adjuvants, and composite materials.

(*Id.* at 20-21 (citation omitted).)

While the Examiner urges that an ordinary artisan would have been prompted to combine Lee's polymers with Tsuru's drug-containing calcium-phosphate granules, the Examiner has not explained why an ordinary artisan would have considered it desirable, or even suitable, to apply a vaccine improvement technique to compositions intended to be used as chemotherapeutics. Absent some explanation in this regard, we are not

persuaded that the cited references would have prompted their combination in the manner posited by the Examiner.

We note Isobe's disclosure that some of the claimed polymers were known to be useful as taste-masking agents for therapeutic compositions orally administered to pets (*see, e.g.,* Isobe, col. 6, ll. 6-24). We are not persuaded, however, that an ordinary artisan would have been prompted to combine a taste-masking agent with either the injected/implantable compositions of Tsuru, or those of Lee.

Accordingly, as we are not persuaded that the Examiner has adequately explained why an ordinary artisan would have combined the cited references' teachings in the manner posited, we reverse the Examiner's obviousness rejection of claim 1, and its dependents.

The Examiner also rejected claims 12 and 13, as obvious over Tsuru, Lee, and Makoto (Ans. 7-8). The Examiner relied on Tsuru and Lee for the teachings discussed above, and further relied on Makoto as evidence that it would have been obvious to use apatite grains having the carbonate concentration required by claims 12 and 13 in Tsuru's drug release compositions (*id.* at 8).

The Examiner does not, however, point to any teaching in Makoto that remedies the deficiency, discussed above, with respect to the Tsuru/Lee combination. We therefore also reverse the Examiner's rejection of claims 12 and 13.

SUMMARY

We reverse the Examiner's obviousness rejection of claims 1-11, 14, 15, 18-20, and 72 over Tsuru, Lee, and Isobe.

We also reverse the Examiner's obviousness rejection of claims 12 and 13 over Tsuru, Lee, and Makoto.

REVERSED

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